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Clonazepam for neuropathic pain and fibromyalgia in adults (Review)

Corrigan R, Derry S, Wiffen PJ, Moore RA

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[Intervention Review]

Clonazepam for neuropathic pain and fibromyalgia in adults

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ABSTRACT

Background

Antiepileptic drugs have been used in pain management since the 1960s; some have shown efficacy in treating different neuropathic pain conditions. Clonazepam, a benzodiazepine, is an established antiepileptic drug, but its place in the treatment of neuropathic pain is unclear.

Objectives

To assess the analgesic efficacy and adverse effects of the antiepileptic drug clonazepam in neuropathic pain and fibromyalgia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2). MEDLINE, and EMBASE to 28 February 2012, together with reference lists of retrieved papers and reviews, and ClinicalTrials.gov.

Selection criteria

We planned to include randomised, double-blind studies of eight weeks duration or longer, comparing clonazepam with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

Data collection and analysis

Two review authors would independently extract data for efficacy and adverse events, and examine issues of study quality.

Main results

We did not identify any studies that satisfied the inclusion criteria.

Authors' conclusions

This review uncovered no evidence of sufficient quality to support the use of clonazepam in chronic neuropathic pain or fibromyalgia.

PLAIN LANGUAGE SUMMARY

Clonazepam for neuropathic pain and fibromyalgia in adults

Nerves which have been damaged by injury or disease can continue to produce pain. This type of pain is called neuropathic pain. Some antiepileptic medications can help neuropathic pain. Clonazepam is an antiepileptic medication, and the aim of this review was to assess how effective clonazepam is for neuropathic pain and fibromyalgia. We identified no good quality studies of clonazepam used in this situation. Dependence and tolerance may occur with prolonged use, although it is less of a problem with clonazepam than many other drugs from the same class (benzodiazepines), and behavioural disinhibition has been reported in a few patients with psychiatric problems. Based on current evidence, clonazepam cannot be recommended for treating neuropathic pain. Other antiepileptic drugs such as pregabalin, gabapentin, and carbamazepine have been shown to be of value in neuropathic pain.

BACKGROUND

Description of the condition

Neuropathic pain, unlike nociceptive pain such as gout and other forms of arthritis, is caused by nerve damage, often accompanied by changes in the central nervous system (CNS). The new (2011) definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011). Fibromyalgia is a complex pain syndrome, defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990), and frequently associated with other symptoms such as poor sleep, fatigue, and depression. More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain (Wolfe 2010). The cause or causes of fibromyalgia are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Cognitive dysfunction is another recently recognised feature of fibromyalgia (Reyes del Paso 2012). Many people with these conditions are significantly disabled with moderate or severe pain for many years. Conventional analgesics are usually not effective, although opioids may be in some individuals. Others may derive some benefit from a topical lidocaine patch or topical capsaicin. Treatment is more usually by unconventional analgesics such as antidepressants or antiepileptics.

Data for the incidence of neuropathic pain are difficult to obtain. However, a systematic review of prevalence and incidence in the Oxford Region of the UK indicates prevalence rates per 100,000 of 34 for postherpetic neuralgia, 400 for diabetic neuropathy and trigeminal neuropathy, and 2000 for fibromyalgia (McQuay 2007). Different estimates in the UK indicate incidences per 100,000 person-years observation of 40 (95% confidence interval (CI) 39 to 41) for post-herpetic neuralgia, 27 (26 to 27) for trigeminal neuralgia, 1 (1 to 2) for phantom limb pain, and 15 (15 to 16) for painful diabetic neuropathy, with rates decreasing in recent years for phantom limb pain and post-herpetic neuralgia and increasing for painful diabetic neuropathy (Hall 2006). The prevalence of neuropathic pain in Austria was reported as being 3.3% (Gustorff 2008). The largest recent study in France found a prevalence of 7% (Bouhassira 2008).

Neuropathic pain and fibromyalgia are difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is now advocated, with physical or cognitive, or both, therapies being combined with pharmacological interventions.

Description of the intervention

Clonazepam is a benzodiazepine, based upon the unusual seven-membered ring and aromatic ring structure that is common to all compounds in this group. Historically, the first benzodiazepine, chlordiazepoxide, was discovered accidentally in the late 1950s as a result of an unplanned reaction at the Roche laboratory, and after routine screening its unexpected pharmacological activity was recognised. Benzodiazepines bind specifically to $GABA_A$ (gamma-aminobutyric acid) receptors at a binding site different to that occupied by GABA, the main inhibitory neurotransmitter in the CNS. Allosteric binding to this ligand-gated ion channel increases its affinity for GABA and therefore facilitates the opening of GABA-activated chloride channels. This enhanced inhibitory response to GABA is thought to be the mechanism behind the main effects of benzodiazepines, namely reduced anxiety, sedation, relaxation of muscle tone, and an anticonvulsant effect.

Clonazepam (trade names: Rivotril and Klonopin) is unusual because it has a very long half-life (approximately 35 hours) and marked anticonvulsant effects with less marked sedation compared to other benzodiazepines. However, as with all benzodiazepines, the generation of tolerance and dependence is of concern. It has also been associated with behavioural disinhibition in patients with psychiatric conditions (e.g. Binder 1987), although other studies have not demonstrated this (e.g. Rothschild 2000). The British National Formulary lists aggression as one of the paradoxical adverse effects (BNF 2011)

Clonazepam is indicated for the treatment of myoclonic, atypical absence, atonic and tonic epileptic seizures, as well as status epilepticus and can be administered orally (4 to 8 mg daily maintenance dose) or intravenously (1 mg/ml ampoules available). Intravenous administration is outside the scope of this review because it is not relevant to chronic treatment. We are unaware of any license for use in neuropathic pain or fibromyalgia.

How the intervention might work

At the molecular level the pathophysiology of both neuropathic pain and fibromyalgia is unclear but both may involve changes to several neurotransmitter systems including those involving substance P, NMDA (N-Methyl-D-aspartic acid), GABA, and opioids. Clonazepam may have a beneficial effect in the treatment of neuropathic pain and fibromyalgia by antagonising hyperexcitability of neurotransmission through the enhancement of inhibitory GABAergic signalling pathways. However, there is no consensus as to both how and even whether clonazepam exerts analgesic effects in these conditions. An earlier Cochrane review, 'Anticonvulsants in acute and chronic pain' (Wiffen 2010) (withdrawn because it is out of date and has been superseded by other reviews of individual drugs, such as this one) found one study in temporomandibular joint dysfunction.

Why it is important to do this review

Some antiepileptic drugs have shown some efficacy in neuropathic pain and fibromyalgia (e.g. gabapentin (Moore 2011), pregabalin (Moore 2009a), and carbamazepine (Wiffen 2011a)), while others do not (e.g. lamotrigine Wiffen 2011b), and for others there are no data (e.g. phenytoin (Birse 2012)). It is important to establish whether clonazepam has a place amongst the available treatment options for these conditions.

There have been several recent changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with the addition of new criteria on what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with "any improvement". Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, and longer trials provide a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment (Moore 2010). To summarise some of the recent insights that make a new review necessary, over and above including more trials, are as follows:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution (see Moore 2005 for acute pain). This is true in acute pain and arthritis (Moore 2009b) as well as in fibromyalgia; in all cases average results usually describe the experience of almost no one in the actual trial. Data expressed as averages are potentially misleading, unless it can be proven that they are suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The IMMPACT group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2009b); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2009b; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009c). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Finally, presently unpublished individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way.

This Cochrane review will therefore assess evidence in ways that make both statistical and clinical sense. Trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally a minimum of 500+ participants in a comparison in which numbers needed to treat to benefit (NNTs) are four or above (Moore 1998)). This does set high standards, and marks a departure from how reviews have been conducted previously.

O B J E C T I V E S

1. To assess the analgesic efficacy of clonazepam for chronic neuropathic pain and fibromyalgia.

2. To assess the adverse events associated with the clinical use of clonazepam for chronic neuropathic pain and fibromyalgia.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We planned to include studies in this review if they were randomised controlled trials (RCTs) with double-blind assessment of outcomes reported after eight weeks of treatment or longer. Full journal publication was required, with the exception of extended abstracts of otherwise unpublished clinical trials. Short abstracts (usually meeting reports) were not included. We excluded studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

Adult participants aged 18 years and above were eligible for inclusion. Participants could have one or more of a wide range of chronic neuropathic pain conditions including:

- painful diabetic neuropathy;
- post-herpetic neuralgia;
- trigeminal neuralgia;
- phantom limb pain;
- postoperative or traumatic neuropathic pain;
- complex regional pain syndrome;
- cancer-related neuropathy;
- Guillain Barré;
- HIV neuropathy;
- spinal cord injury; or
- fibromyalgia.

Studies of participants with more than one type of neuropathic pain would also be included. We planned to analyse results according to the primary condition.

Types of interventions

Clonazepam in any dose, administered orally or intravenously for the relief of neuropathic pain or fibromyalgia, and compared to placebo, no intervention or any other active comparator. Studies using clonazepam to treat pain resulting from the use of other drugs were not included.

Types of outcome measures

We anticipated that a variety of outcome measures would be used in the studies. The majority of studies were expected to use standard subjective scales for pain intensity or pain relief, or both. Particular attention would be paid to IMMPACT definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes are different from those set out in an earlier review of antidepressants for neuropathic pain (Saarto 2007), concentrating on dichotomous outcomes where pain responses are not normally distributed.

Primary outcomes

1. Patient-reported pain relief of 30% or greater.
2. Patient-reported pain relief of 50% or greater.
3. Patient-reported global impression of clinical change (PGIC) much or very much improved.
4. Patient-reported global impression of clinical change (PGIC) very much improved.

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event.
5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence and dizziness.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 2);
- MEDLINE (via Ovid) (to 28 February 2012);
- EMBASE (via Ovid) (to 28 February 2012).

See Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the CENTRAL search strategy.
There was no language restriction.

Searching other resources

We searched the reference lists of retrieved articles and reviews, and ClinicalTrials.gov, for any relevant studies.

Data collection and analysis

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors read these studies independently and reached agreement on inclusion by discussion. The studies were not anonymised in any way before assessment.

Data extraction and management

We planned that two review authors would independently extract data using a standard form, and agree results before entry into RevMan 5 (RevMan 2011) or any other analysis method. Data extracted would include information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event, or any serious adverse event).

Assessment of risk of bias in included studies

We planned to complete a 'Risk of bias' table to report on sequence generation, allocation concealment, blinding, and other risks such as size and imputation method for missing data.

Measures of treatment effect

We planned to calculate numbers needed to treat to benefit (NNTs) as the reciprocal of the absolute risk reduction (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat to harm (NNH), and is calculated in the same manner. Dichotomous data would be used to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below). We did not plan to use continuous data because it is inappropriate where there is an underlying skewed distribution.

Unit of analysis issues

We would accept randomisation to individual participants only. The control treatment arm would be split between active treatment arms in a single study if the active treatment arms were not combined for analysis.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis. The ITT population would consist of participants who were randomised, took the assigned study medication, and provided at least one post-baseline assessment. Missing participants would be assigned zero improvement.

Assessment of heterogeneity

Clinical heterogeneity would be dealt with by combining studies that examine similar conditions. Statistical heterogeneity would be assessed visually (L'Abbé 1987) and with the use of the I^2 statistic. If I^2 was greater than 50%, reasons would be sought.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2009b). The review would not depend on what authors of the original studies chose to report or not, though clearly there would be difficulties with studies failing to report any dichotomous results. Continuous data, which probably poorly reflect efficacy and utility, would be extracted and used only if useful for illustrative purposes.
We undertook no formal assessment of publication bias.

Data synthesis

We planned to use a fixed-effect model for meta-analysis. A random-effects model would be used if there was significant heterogeneity and it was considered appropriate to combine studies.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be undertaken for:

- dose of clonazepam;
- different painful conditions.

Sensitivity analysis

No sensitivity analyses were planned because the evidence base is known to be too small to allow reliable analysis. We would not pool results from neuropathic pain of different origins.

RESULTS

Description of studies

Results of the search

The search identified three studies which we considered for inclusion.

Included studies

None of the studies identified by the search strategy met the inclusion criteria set out in this review.

Excluded studies

We considered but excluded three studies. All studies were excluded as the duration of treatment was less than the eight weeks stipulated in the inclusion criteria. Furthermore we considered the pain syndromes investigated by these studies (temporomandibular joint dysfunction (Harkins 1991), burning mouth syndrome

(Gremeau-Richard 2004), and jaw pain upon wakening (Herman 2002)) beyond the scope of this review. Finally, we also considered the topical application of clonazepam investigated by Gremeau-Richard 2004 to breach the inclusion criteria.

Risk of bias in included studies

There were no included studies to assess.

Effects of interventions

There were no included studies to assess.

DISCUSSION

Summary of main results

The literature search did not reveal any studies that met the inclusion criteria laid out in the protocol for this review. The inclusion criteria used here are based on modern standards for assessing the efficacy of pharmacological agents in neuropathic pain and the lack of studies fit for inclusion reflects the lack of recent interest in the systemic use of clonazepam in this context.

One paper (Gremeau-Richard 2004) assessed the use of topical clonazepam for the treatment of burning mouth syndrome (stomatodynia). This paper failed to meet the inclusion criteria for several reasons. Firstly both stomatodynia and topical application of clonazepam (as opposed to oral or intravenous administration of systemic clonazepam) are considered outside the scope of this review, and secondly the intervention period was just 14 days which is much shorter than the eight-week period stipulated by the inclusion criteria of this review. Of interest, however, this study found that patients who sucked a lozenge containing 1 mg of clonazepam for three minutes three times per day for 14 days experienced significantly less pain than those given placebo when assessed five minutes after finishing the lozenge, as measured using a 14-point numerical scale. At least 50% pain relief was experienced by 11/24 participants with clonazepam and 3/24 with placebo, using an ITT) analysis. Three participants left the study due to side effects (sleepiness) or perceived lack of effectiveness.

Two further studies (Harkins 1991; Herman 2002) addressed the use of clonazepam for the treatment of two further pain conditions considered outside the scope of this review.

The first, a pilot study (Harkins 1991), investigated the effect of clonazepam on pain caused by temporomandibular joint dysfunction. Oral clonazepam was administered daily for 60 days (at a maximum dose of 1 mg/day). Pain was assessed at baseline, day 30, and day 60 using a visual analogue scale (VAS) to report both pain felt upon palpitation of specific sites by the examiner and perceived global pain levels of the head and neck. High drop-out rates in both the placebo and clonazepam groups (due to a perceived lack of improvement, or a perceived significant improvement, respectively) limited analysis in this study to just 30 days. However, at 30 days of clonazepam treatment both measures of pain were significantly reduced compared to placebo (approximately 40% to 50% reduction in reported pain after clonazepam treatment versus approximately 0% to 10% reduction in the placebo group).

The second (Herman 2002, 41 participants) compared the effectiveness of clonazepam and cyclobenzaprine to placebo in the treatment of jaw pain upon wakening. After three weeks of 0.5 mg clonazepam neither the patients' reported pain upon wakening, assessed using a VAS, nor sleep quality, measured using the Pittsburgh Sleep Quality Index differed significantly from placebo.

As well as studying pain conditions outside the scope of this review, the intervention periods of the studies reported in both of these papers are also too short to meet the inclusion criteria of this review, and the numbers of participants treated were too small to permit any conclusions about efficacy.

Although these three studies were excluded here, Harkins 1991 and Gremeau-Richard 2004 have been included in previous reviews which discuss the role of clonazepam in the pharmacological management of neuropathic pain.

Overall completeness and applicability of evidence

We carried out an extensive literature search. It is unlikely that we have missed substantial amounts of relevant data.

Agreements and disagreements with other studies or reviews

Martin 2011 reviewed RCTs) of anticonvulsant drugs in the management of orofacial pain (including neuropathic pain). This review includes Gremeau-Richard 2004 which it declares to be of "high quality", yet the inclusion of only eight studies (of which only six were randomised controlled trials) analysing pain relief in five conditions limits the authors to conclude that there is insufficient evidence regarding the efficacy of anticonvulsants in orofacial pain disorders, with the exception of carbamazepine for the treatment of trigeminal neuralgia. Similarly, Gremeau-Richard 2004 is included in Patton 2007, which concludes that topical clonazepam and oral capsaicin are the only treatments for burning mouth syndrome that have robust placebo-controlled RCT evidence supporting their usage, with the caveat that in each case it is just one trial, and contrary to the many other treatments used in clinical practice.

McQuay 1995 reviewed RCTs of anticonvulsant drugs in the management of acute, chronic, or cancer pain. The review was not, however, limited to neuropathic pain and includes a study of clonazepam in migraine prophylaxis. Despite including Harkins 1991 the review concludes that more studies are required in order to provide persuasive high-quality evidence.

Tremont-Lukats 2000 described five studies of the use of clonazepam in the treatment of chronic neuropathic pain conditions dating back to 1975, all of which demonstrated good improvements in the pain response. However, none of the studies included in this paper are RCTs.

Not all recent systematic reviews of RCTs for the use of anticonvulsants to treat neuropathic pain include the studies relating to clonazepam. For example, the three reviews Finnerup 2010, Chou 2007 and Jensen 2009 review the comparative efficacy of drugs and different drug classes in the treatment of neuropathic pain but do not include any references to clonazepam.

Dworkin 2008 reviews current guidelines for treatment of neuropathic pain and discusses how recent studies should influence future guidelines. The authors make no reference to clonazepam or other anticonvulsants but raise the point that inadequate power of studies testing pharmacological agents against placebo in neuropathic pain renders them unhelpful in extrapolating their true efficacy. They conclude, much like this review, that to inform future treatment guidelines, high-quality RCTs must be conducted that directly compare medications for neuropathic pain with each other and placebo, providing a superior evidence base than currently exists.

Finally, clonazepam does not feature on the list of pharmacological treatments considered for the clinical guideline on neuropathic pain (NICE 2010). The American Association of Neurology guidelines for the treatment of painful diabetic neuropathy make no mention of the use of clonazepam in this context (AAN 2011).

AUTHORS' CONCLUSIONS

Implications for practice

This review has uncovered no evidence of sufficient quality to support a rationale for the use of clonazepam in chronic neuropathic pain and fibromyalgia, and the possibility of adverse effects is likely to curtail any potential use in these conditions. Other antiepileptic drugs such as pregabalin, gabapentin, and carbamazepine have been shown to be of value in neuropathic pain, and should be used in preference.

Implications for research

If clonazepam is to be considered for use in this context, high-quality, randomised, double-blinded, placebo-controlled trials need to be carried out to build a base of evidence supporting its use or confirming it to be ineffective. Clonazepam is an old drug and this seems unlikely to occur due to the cost of such studies and the lack of financial incentive behind them, in this case because clonazepam is out of patent and there would be little or no profit to justify the large trial costs.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gremeau-Richard 2004	Treatment period of insufficient duration - 14 days, burning mouth syndrome, topical application
Harkins 1991	Treatment period of insufficient duration - 30 days, temporomandibular dysfunction
Herman 2002	Treatment period of insufficient duration - 3 weeks, jaw pain upon awakening

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp PAIN/
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/
3. exp SOMATOSENSORY DISORDERS/
4. FIBROMYALGIA/ or exp MYOFASCIAL PAIN SYNDROMES/ or POLYMYALGIA RHEUMATICA/
5. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
6. (fibromyalgi* or fibrosti* or FM or FMS).mp.
7. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Clonazepam.mp.
10. (Rivotril or Klonopin).mp.
11. 9 or 10
12. 8 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 23 and 12

Appendix 2. EMBASE search strategy

1. exp chronic pain/
2. exp peripheral neuropathy/
3. exp somatosensory disorder/
4. fibromyalgia/ or exp myofascial pain/ or rheumatic polymyalgia/
5. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
6. (fibromyalgi* or fibrosti* or FM or FMS).mp.
7. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. clonazepam.mp.
10. (Rivotril or Klonopin).mp.
11. 9 or 10
12. 8 and 11
13. random*.ti,ab.
14. factorial*.ti,ab.
15. (crossover* or cross over* or cross-over*).ti,ab.
16. placebo*.ti,ab.
17. (doubl* adj blind*).ti,ab.
18. assign*.ti,ab.
19. allocat*.ti,ab.
20. RANDOMIZED CONTROLLED TRIAL.sh.
21. DOUBLE-BLIND PROCEDURE.sh.
22. CROSSOVER PROCEDURE.sh.
23. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 12 and 23

Appendix 3. CENTRAL search strategy

1. MeSH descriptor Pain explode all trees
2. MeSH descriptor Peripheral Nervous System Diseases explode all trees
3. MeSH descriptor Somatosensory Disorders explode all trees
4. MeSH descriptor Fibromyalgia this term only
5. MeSH descriptor Myofascial Pain Syndromes explode all trees
6. MeSH descriptor Polymyalgia Rheumatica explode all trees
7. ((pain* or discomfort*) and (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)):ti,ab,kw
8. (fibromyalgi* or fibrosti* or FM or FMS):ti,ab,kw
9. ((neur* or nerv*) and (compress* or damag*)):ti,ab,kw
10. (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9)
11. clonazepam:ti,ab,kw
12. (Rivotril or Klonopin):ti,ab,kw
13. 11 or 12
14. 10 and 13
15. Limit 14 to CENTRAL

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected

HISTORY

Protocol first published: Issue 12, 2011

Review first published: Issue 5, 2012

Date	Event	Description
18 July 2013	Review declared as stable	This review will be assessed for further updating in 2020 as it is unlikely that new evidence will be published

CONTRIBUTIONS OF AUTHORS

RAM and SD wrote the protocol. RC and SD carried out searches and assessed studies for inclusion. RC and SD planned to extract data and carry out analyses. RAM acted as arbitrator. All authors were involved in writing the review.

DECLARATIONS OF INTEREST

SD and RAM have received research support from charities, government, and industry sources at various times. RAM has consulted for various pharmaceutical companies, and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. PW is a full-time employee of the UK Cochrane Centre, funded by the UK National Institute of Health Research and has no relevant interests to declare. RC has no interests to declare. No company with any interest in clonazepam had any involvement in the production of this review.

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Anticonvulsants [*therapeutic use]; Clonazepam [*therapeutic use]; Fibromyalgia [*drug therapy]; Neuralgia [*drug therapy]; Pain Management [*methods]

MeSH check words

Adult; Humans